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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,455	04/05/2006	Moise Azria	PA/4-33288A	9884

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,455	AZRIA ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,9,10,17,18 and 24-29* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,9,10 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090728*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The Information Disclosure Statement (IDS) filed 28 July 2009 has been entered. Applicant's amendment of the claim filed 28 July 2009 has been entered. Applicant's remarks submitted on 28 July 2009 are acknowledged.

Claims 2-5, 7, 8, 11-16 and 19-23 are cancelled. Claims 24-29 have been added. Claims 1, 6, 9, 10, 17, 18 and 24-29 are pending. Claims 17 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1, 6, 9, 10 and 24-29 are under examination.

Claim Rejections Withdrawn

The rejection of claims 1-2, 5-6 and 9-10 under 35 U.S.C. 103(a), as being unpatentable over Ghirri et al. (US 6,352,974 B1) in view of Bay et al. (US 20020065255 A1), is withdrawn in response to Applicant's argument that Ghirri et al. discloses a broad range of potential doses, which can not render the instantly claimed dose range obvious. In addition, the claims of the instant invention have been amended

to recite further narrower doses of 0.4-1.2 mg, 0.8-1.2 mg, or about 1 mg of salmon calcitonin.

The provisional rejection of claim 2 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9 and 10 of copending Application No. 11/577,127, is withdrawn in response to Applicant's cancellation of the claim.

Claim Rejections Maintained

Double Patenting

Claim 1 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28 and 29 of copending Application No. 12/093,383.

Claims 1, 9, 10 and new claims 24-29 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-15 of copending Application No. 12/132,642.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The basis of these provisional nonstatutory obviousness-type double patenting rejections has been set forth in the previous office action (mailed 10/6/2008) and as the following. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 28 and 29 of copending Application No. 12/093,383 are directed to a method of treating an arthritic disease, e.g., osteoarthritis, in a patient in need thereof, comprising administering an oral pharmaceutical composition comprising a poly(amino acid), e.g., salmon calcitonin, and a delivering agent, e.g., 5-CNAC. Claims 13-15 of copending Application No. 12/132,642 are directed to a method of treatment of bone related diseases and calcium disorders comprising administering to a patient in need of such treatment a composition suitable for oral delivery which comprises a calcitonin, e.g., salmon calcitonin, and a delivery agent in micronized form that have a generic structure shown in Formula I (Formula I encompasses a disodium salt of 5-CNAC, SNAD or SNAC). The methods of the copending applications differ from the instant application in that the instant application is drawn to a method of treating osteoarthritis comprising orally administering to a human in need thereof a pharmaceutical composition comprising between 0.4-1.2 mg of salmon calcitonin, and a delivery agent, e.g., 5-CNAC, SNAD, or SNAC. The salmon calcitonin dosages recited in the instant claims are taught in Stern et al. (U. S. Patent No: 5,912,014, Date of Patent: Jun. 15, 1999) (also see the following 35 USC § 103 section). Stern et al. teaches using dosages of salmon calcitonin ranging between 0.1-1 mg for treating bone-related diseases (col. 9, line 65 bridging col. 10, line 3). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made to modify the methods of the copending applications by using 0.1-1 mg of salmon calcitonin for treating the arthritic or bone-related diseases. One of ordinary skill in the art would have been motivated to do so, because Stern et al. teaches that salmon calcitonin at this dosage range is effective for the treatment of the diseases. Such a modification provides a reasonable expectation of successfully treating the diseases. Because the instant claims are either anticipated by, or would have been obvious over, the reference claims, an obviousness-type double patenting rejection is appropriate.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant argues that the present application is further along in prosecution than the above-identified co-pending applications. Applicant requests that upon allowance of the claims under consideration in this application, the double patenting rejection in this application will be withdrawn, and a provisional double patenting rejection will be made in the above-identified co-pending applications, which may then be converted into a double patenting rejection upon the present application issuing into a patent.

The instant claims, however, are not in condition for allowance (see the following). Therefore, the provisional obviousness-type double patenting rejections are maintained.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 9, 10 and 24-29 are rejected under 35 U.S.C. 103(a), as being unpatentable over Stern et al. (U. S. Patent No: 5,912,014, Date of Patent: Jun. 15, 1999), in view of Kaplan et al (J. Am. Acad. Orthop. Surg., 1995, Vol. 3(6):336-344), and further in view of Bay et al. (US 20020065255 A1, Pub. Date: 30 May 2002, reference provided previously).

The instant claims are directed to a method of treating osteoarthritis in a human in need thereof comprising orally administering a pharmaceutical composition comprising salmon calcitonin in free or salt form in an amount of 0.4-1.2 mg, or 0.8-1.2 mg, or about 1 mg, and a delivery agent selected from the group of 5-CNAC, SNAD, SNAC and disodium salts thereof (claims 1, 9, 24-29); wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable pH-lowering agent, at least one absorption enhancer, and an enteric coating (claim 6); and wherein the delivery agent is in micronized form (claim 10).

Stern et al. teaches the use of an oral pharmaceutical composition comprising salmon calcitonin for treating patients with osteoporosis, Paget's disease, and the like (col. 3, 1st paragraph). Stern et al. teaches that the pharmaceutical composition for oral delivery of salmon calcitonin further comprises at least one pharmaceutically acceptable pH-lowering agent, at least one absorption enhancer effective to promote bioavailability

of salmon calcitonin, and an enteric coating (col. 1, line 65 bridging col. 2, line 18). Stern et al. teaches the pharmacokinetics of salmon calcitonin in the treatment of human patients (col. 9, paragraphs 1 and 2 under section "Treatment of Patients"), and describes that because salmon calcitonin may cause gastrointestinal distress in some patients when serum concentration reaches at high peak levels (e.g., at 200 pg/ml), it is preferred that serum salmon calcitonin peaks between 10-150 pg/ml, more preferably between 10-50 pg/ml (col. 9, lines 52-57). Stern et al. further teaches that the oral pharmaceutical composition permits delivery of salmon calcitonin into the blood at the above-identified preferred concentration levels while using only 100-1000 μg (i.e., 0.1-1 mg) of salmon calcitonin per capsule (col. 9, line 65 bridging col. 10, line 3).

Stern et al. teaches as set forth above. Stern et al., however, does not expressly teach treating osteoarthritis, nor teaches that the oral pharmaceutical composition comprises a delivery agent selected from the group consisting of 5-CNAC, SNAD, SNAC, and said delivery agent is in micronized form, and is a disodium salt thereof, e.g., a disodium salt of 5-CNAC.

Kaplan et al. teaches clinical manifestations and complications of Paget's disease, which includes osteoarthritis (pp. 339, Table 2).

Bay et al. teaches adding a delivery agent, such as a disodium salt of 5-CNAC, SNAD, or SNAC, into pharmaceutical compositions comprising an active agent, e.g., salmon calcitonin [0010] [0015] [0035]. Bay et al. teaches that the disodium salt of 5-CNAC, SNAD, or SNAC has greater efficacy for delivering the active agent than the corresponding monosodium salt and free acid [0009]. Bay et al. teaches that the

pharmaceutical compositions may be formulated into an oral dosage unit form, e.g., particles, powders or sachets (micronized forms) [0015] [0042].

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add a disodium salt of 5-CNAC, SNAD, or SNAC into the oral salmon calcitonin pharmaceutical composition for treating patients having osteoarthritis secondary to Paget's disease. One of ordinary skill in the art would have been motivated to do so, because Stern et al. teaches that the oral salmon calcitonin pharmaceutical composition is useful for treating Paget's disease, Kaplan et al. teaches that these patients have osteoarthritis as clinical manifestations, and Bay et al. further teaches adding the disodium salt of 5-CNAC, SNAD, or SNAC to increase efficacy for delivering the salmon calcitonin in oral pharmaceutical compositions. Therefore, the combined teachings provide a reasonable expectation of successfully delivering the salmon calcitonin for the therapeutic treatment.

In the response received on 28 July 2009, Applicant argues that Bay shows in the Examples a very large dose of salmon calcitonin provided to monkeys (e.g., 800 μg), and to rats (e.g., 25 mg/kg-4000 mg/kg), in order to orally deliver salmon calcitonin and achieve the salmon calcitonin serum concentrations. Applicant argues that Bay teaches that a very large dose of salmon calcitonin is required in combination with, e.g., 5-CNAC, to achieve pharmaceutically acceptable levels of salmon calcitonin *in vivo* when calcitonin is delivered orally. Applicant argues that in contrast, the claimed method requires only between 0.4-1.2 mg, 0.8-1.2 mg, or about 1 mg of salmon.calcitonin in

free or salt form when salmon calcitonin is used in combination with the recited delivery agents. Applicant argues that Bay teaches away from using the doses recited in Applicant's method, and the Office may not simply ignore the large amounts of calcitonin taught by Bay for oral delivery when using 5-CNAC, SNAD, or SNAC as the delivery agent. Applicant argues that the doses of salmon calcitonin used in Bay's examples, when translate to a human dose (based on average body weight), is equivalent to 11 mg (using the monkey dose), or 1.75-280 g (using the rat doses).

Applicant also argues that oral delivery of proteins is extremely difficult to achieve, and hence extremely unpredicatable. Applicant argues that oral delivery of proteins faces hurdles, such as circumventing the natural degradation and digestion of proteins in the gut of an intended patient, and poor bioavailability and absorption. Applicant argues that Bay provides no evidence that the salmon calcitonin compositions would result in what Applicant claims, i.e., treating osteoarthritis. Applicant argues that Bay's successful delivery of salmon calcitonin to a rat or a monkey tells nothing about whether that delivery and dose actually result in treatment of a human. Applicant argues that the present application demonstrates for the first time that calcitonin can be orally delivered in combination with 5-CNAC, SNAD or SNAC to humans; and is efficacious in the treatment of osteoarthritis in humans. Applicant further argues that the experimental results on page 26 show the unexpected beneficial results.

Applicants' argument has been fully considered but has not been found to be persuasive.

As stated above, the dosages recited in the presently claimed method are taught and suggested by Stern et al. The dosage range taught by Stern et al. is not broad, and most importantly, it is based on the pharmacokinetics of salmon calcitonin in the treatment of human patients. Stern et al. teaches that because salmon calcitonin may cause gastrointestinal distress in some patients when serum concentration reaches at high peak levels (e.g., at 200 pg/ml), it is preferred that serum salmon calcitonin peaks between 10-150 pg/ml, more preferably between 10-50 pg/ml. Stern et al. discloses an oral salmon calcitonin pharmaceutical composition which permits delivery of salmon calcitonin into the blood at the above-identified preferred concentration levels while using only 0.1-1 mg of salmon calcitonin per capsule. Stern et al. teaches that the successful delivery of salmon calcitonin into the blood at the preferred serum levels is achievable because of the use of additives, for example, at least one pharmaceutically acceptable pH-lowering agent, which protects proteolytic degradation of salmon calcitonin by intestinal or pancreatic proteases, at least one absorption enhancer, which promotes bioavailability of salmon calcitonin, and an enteric coating, which prevents contact between stomach proteases and salmon calcitonin. Thus, even though it is difficult and unpredictable to orally deliver protein drugs, such as salmon calcitonin, Stern et al. has demonstrated successfully delivering salmon calcitonin into blood of human patients to achieve the desirable serum levels through the use of additives to overcome hurdles like poor bioavailablity and absorption, as well as protein degradation. Furthermore, Stern et al. teaches using the oral pharmaceutical composition for treating Paget's disease, which clinical manifestations include

osteoarthritis. Therefore, Stern et al. teaches using oral salmon calcitonin pharmaceutical compositions with the same dosage range for treating the same patients.

Stern et al., however, does not teach adding 5-CNAC, SNAD, SNAC, or a disodium salt thereof, in micronized form, into the compositions. This deficiency is cured by Bay et al. (see above). With respect to Applicant's argument regarding the large doses used in Bay et al.'s examples, first, the instant claims do not recite the dosage as "mg/kg", it is therefore inappropriate to simply translate the monkey dose, e.g., 800 μg, into a human dose (11 mg) based on relative body weights. Further, even the rat doses are expressed as "mg/kg", no one in the art would use a rat "mg/kg" dose for a human. Second, the purpose of Bay's disclosure is to improve oral delivery, thus, the dosages used in the examples were designed to examine the effects of different additives on protein delivery. It is, again, inappropriate to assert that such dosages "teaches away" from that used for a disease treatment, e.g., bone related disorders. Bay et al. teaches adding 5-CNAC into several oral pharmaceutical compositions containing a protein drug, including salmon calcitonin, for improving delivery. Bay et al. teaches that the formulation containing 5-CNAC can be in a micronized (powdered) form. Bay et al. further teaches that the disodium salt of 5-CNAC provides greater efficacy for delivering the active agent than the corresponding monosodium salt and free acid. Therefore, it is *prima facie* obvious to one of ordinary skill in the art to add 5-CNAC into the oral salmon calcitonin pharmaceutical composition disclosed in Stern et al.

With respect to the unexpected results described on page 25-26 of the instant specification, the components of the compositions used in different treatment groups are identical (e.g., each composition contains the same amount and form of 5-CNAC), except that salmon calcitonin concentrations are different. Thus, even the results show different benefit among the dosages used, there is no comparison for the benefit of the delivery agent.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
/Xiaozhen Xie/
September 11, 2009